New protein could prove powerful target for cholesterol lowering drugs

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A protein has been discovered that may have a profound effect on cholesterol metabolism. That discovery raises the possibility that the protein, dubbed IDOL, could be a powerful target for cholesterol-lowering drugs, says corresponding author Peter Tontonoz of the Howard Hughes Medical Institute and the University of California, Los Angeles. The research is published in the May 2011 edition of the journal *Molecular and Cellular Biology*.

The mechanism is simple. The major regulator of cholesterol levels in the blood is the low density lipoprotein receptor. It controls blood cholesterol levels by transporting cholesterol from the blood into the cells. Tontonoz and his collaborators recently discovered that IDOL can break down low density lipoprotein receptors, thus preventing them from removing cholesterol from the blood. (IDOL stands for Inducible Degrader Of the Low-density lipoprotein receptor.)

In the study, in order to test their hypothesis that interfering with IDOL could boost cholesterol transport out of the blood, the researchers developed and characterized embryonic stem cells that lack the IDOL gene. “We showed that cells lacking IDOL exhibit markedly elevated levels of the low density lipoprotein receptor protein, and increased rates of low density lipoprotein uptake by the cells,” says Tontonoz. They also found that absent IDOL, the lifetimes of low density lipoprotein receptors are prolonged. They demonstrated further that the increases in low density lipoprotein receptor caused by the absence of IDOL, and by statin drugs are additive, suggesting that inactivating IDOL might

ultimately enhance statins' cholesterol lowering effects in humans.

A further finding is that IDOL functions independently of another protein previously known to regulate low density lipoproteins, called PCSK9.

"Our study raises the possibility that IDOL could be a target for drugs to lower human cholesterol levels; however, future work is needed to test this idea," says Tontonoz. "Our current study analyzed only cells that lack IDOL. An important next step is to analyze whole mice that lack IDOL in order to determine the importance of IDOL in vivo."

Despite the negative effects too much blood cholesterol has to cardiovascular health, this compound plays critical roles in living systems, including as a precursor to steroid hormones, and in developmental signaling, and control of membrane fluidity.

More information: E. Scotti, et al., 2011. Targeted disruption of the idol gene alters cellular regulation of the low-density lipoprotein receptor by sterols and liver X receptor agonists. *Mol. Cell. Biol.* 31:1885-1893

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